I. Information Disclosure Statement

The Examiner is correct. The Supplemental Information Disclosure Statement mailed May 22, 2000, provided **three**, rather than four, English-language patent documents equivalent to the foreign patent documents cited in the Information Disclosure Statement mailed November 18, 1999.

II. Objection to Claims

Claims 16 and 23 were objected to for allegedly failing to further limit claim 15. Applicant respectfully traverses the objection.

The method of applicant's claim 15 requires (1) preparing an alkali metal salt, and then (2) coating the prepared alkali metal salt onto the inner cores of the composition. Claim 16 requires that, in the method of claim 15, the alkali metal salt be formed in the **same** solution used in the coating process. In contrast, claim 23 requires that the alkali metal salt be **recovered in a solid form before** coating onto the inner cores. One cannot possibly carry out the processes of both claims 15 and 23 simultaneously. It is also clear that claim 15 is generic to both claims 15 and 23.

Whether the interaction of acid and metal in step (1) must take place in solution is completely irrelevant in determining whether claims 16 or 23 further limit claim 15. The Examiner appears to miss the point by focusing on "the manner in which the salt is prepare." The primary difference between claim 15 and claims 16 or 23 is what occurs **after** the salt is prepared and **before** the salt is coated onto the inner cores, that is, whether the solution is used

directly in the coating process or whether the salt is recovered from that solution prior to coating onto the cores.

The Examiner's argument that the way in which the "salt is made is not seem to be of patentable import" is entirely improper! That is clearly not a proper basis for assessing whether a dependent claim further limits an independent claim. Nonetheless, in a **process** claim, the manner in which the salt or salt solution is formed clearly can be pertinent to the scope of the claim and hence its patentability. Moreover, the *degree* of further limitation or *non-obviousness* of the further limitation must not factor into an analysis as to whether a further limitation exists. Clearly claims 16 or 23 further limit the process of claim 15. That is all the patent law and rules require. The objection to claims 16 and 23 is improper and should be withdrawn.

III. Rejections under 35 U.S.C. § 103

Claims 1-17, 19, and 21-28 were rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,376,384 to Eichel et al. ("Eichel") in view of U.S. Patent No. 5,180,832 to Freyne et al. ("Freyne"). Applicant respectfully traverses the rejections.

Applicant's Claimed Compositions and Methods

Applicant has developed improved compositions for the controlled delivery of drug to the colon. The claimed composition includes pellets having (1) an inner core including a drug and (2) a rate-controlling membrane coating the inner core; and requires (3) a means to prevent release of the drug until the composition reaches the terminal ileum or colon following oral

administration of the composition. Applicant also developed methods for making these compositions.

Eichel, Alone or in Combination with Freyne,

Fails to Suggest Applicant's Compositions and Methods

Eichel discloses a drug delivery composition with a coating comprising a controlled release polymer, such as ethyl cellulose or acrylic resin, and an additive that is incorporated into the coating. It is the additive that controls the rate of hydration and permeability of the coating (see col. 4, lines17-22). These compositions are not adapted to **prevent** release **until** the composition reaches the terminal ileum or colon. Eichel's disclosure of *sustained*, delayed release for about 2 to 10 hours after ingestion does not provide any motivation to one of ordinary skill in the art that he or she should prevent release *until* the composition reaches the terminal ileum or colon. Inevitably, in some instances (if not all instances), the Eichel compositions will release drug *before* reaching the terminal ileum or colon. The fact that some drug may not be released until reaching the colon is not a teaching to prevent release before reaching the colon, absent improper hindsight reconstruction based on applicant's disclosure.

Eichel further fails to disclose or suggest using the composition to provide delivery of an alkali metal salt of a weak acid. In contrast, one of the primary objectives of the present invention is to provide new formulations for the delivery of weak acid drugs (see page 1, lines 3-4 of applicant's specification). Applicant met this objective by providing the weak acid drug in the form of a plurality of sustained-release pellets targeted for delivery to the colon, and in the

form of a salt. Applicant surprisingly found that when weak acid drugs, such as ridogrel, are provided to the colonic region (**specifically**) in this form, the drug release profile is not only pH independent (see, *inter alia*, page 4, line 29 to page 5, line 2; examples in specification), but is also zero order (see, *inter alia*, Figure 5) and provides for good dispersion of drug in the colon (see, *inter alia*, page 3, lines 20-22). Nothing in Eichel, alone or in combination with Freyne, would motivate one of ordinary skill in the art to make a composition for the delivery of weak acid drugs at all, let alone one that is adapted for specific delivery to the colon.

Furthermore, those of ordinary skill in the art are provided with absolutely no motivation whatsoever to provide such a composition in the form of a plurality of sustained release pellets in which the drug is provides in the form of a salt. Eichel and Freyne provide no guidance for making the claimed compositions or for implementing the claimed methods of manufacture therefor.

The Court of Appeals for the Federal Circuit recently warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. WMS Gaming, Inc. v International Game

Technology, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "**The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.**" In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999) (emphasis added). The Examiner has not provided the required clear and particular showing that the prior art as a whole suggests the desirability, and thus the obviousness, of making the claimed combination of elements. Thus, no *prima facie* case of obviousness has been established.

Applicant therefore is not *required* to set forth objective evidence of nonobviousness. Applicant nonetheless has described in the specification the **unexpected** advantages, as explained above, provided by the claimed compositions. These advantages are evidence of non-obviousness; nothing in the cited art suggests them.

In response to the allegation that no arguments have been made with respect to the method claims, applicant explicitly reiterates that claims 15-17 and 19 are patentable for essentially the same reasons described herein and in the remarks accompanying the Amendment mailed May 22, 2000, with respect to the composition claims. As the compositions are novel and nonobvious, so are methods of making said compositions, particularly the methods recited in claims 15-17 and 19.

The pending claims are thus novel and nonobvious over the prior art of record.

Allowance of claims 1-14 and 21-28 is therefore earnestly solicited.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Eva Mukasa

Date: November 28, 2000

Appendix

Claims as Pending

1. (Once amended) A controlled release composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release,

wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and

wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

2. (Once amended) The composition of claim 1 wherein the drug is a thromboxane synthase A_2 inhibitor or a thromboxane A_2/prostaglandin endoperoxide receptor antagonist.

3. (Once amended) The composition of claim 2 wherein the drug is ridogrel.

4. (Once amended) The composition of claim 1 wherein the rate-controlling membrane comprises a material which forms a water-insoluble, but water-permeable layer and from which release of the drug is by diffusion through the layer.

5. (Once amended) The composition of claim 4 wherein the rate-controlling membrane is formulated from a methacrylate copolymer or ethylcellulose.

6. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is formulated from EUDRAGIT™ NE30D.

7. (Once amended) The composition of claim 5 wherein the rate-controlling membrane is ethylcellulose.

8. (Once amended) The composition of claim 1 wherein the inner core is a sugar sphere.

9. (Once amended) The composition of claim 1 wherein the salt is at least 10 times more soluble than the free acid form of the drug at pH 4.5 to 8.0 at 37 °C.

10. (Amended) The composition of claim 9 wherein the salt is at least 100 times more soluble than the free acid form of the drug.

11. (Once amended) The composition of claim 1 wherein the salt is an alkali metal salt.

12. (Once amended) The composition of claim 11 wherein the alkali metal is sodium or potassium.

13. (Once amended) The composition of claim 1 wherein the pellets are administered in a starch capsule coated with a combination of polymethacrylates that is designed to disintegrate and release the pellets in the terminal ileum or in the colon.

14. (Once amended) The composition of claim 1 wherein the drug is used for a treatment selected from the group consisting of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and inflammatory bowel disease.

15. (Once amended) A method for making a composition comprising pellets, wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition, the method comprising

making a salt of the drug, and

coating the salt onto the inner cores.

16. (Twice amended) The method of claim 15 wherein the salt is made in a solution used in the coating of the inner cores.

17. (Once amended) A method of improving the controlled release profile of a drug with a rapidly changing solubility in the pH range 4.5 to 8.0, the method comprising

administering the drug in a composition comprising pellets,

wherein each pellet comprises an inner core comprising the drug which possesses

(a) a free acid group which can be converted into an alkali metal salt and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

18. (Cancelled).

19. (Once amended) A method of treatment of ulcerative colitis, Crohn's disease, irritable bowel syndrome, and/or inflammatory bowel disease, the method comprising

administering to a patient in need of treatment a composition comprising pellets,

wherein each pellet comprises an inner core comprising a drug which possesses

(a) a free acid group which can be converted into an alkali metal salt, and

(b) a pKa in the range 2.0 to 9.0,

wherein the inner core is coated with a rate-controlling membrane that determines drug release, wherein the drug is present as a salt that displays higher solubility at pH 4.5 to 8.0 than the corresponding compound containing a free acid group, and wherein the composition is adapted to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

20. (Cancelled).

21. The composition of claim 1 wherein the pellets are compressed into tablets which are coated to prevent release of drug until the composition reaches the terminal ileum or the colon following oral administration of the composition.

22. The composition of claim 1 wherein the core is between about 0.3 to 5 mm in size.

23. The method of claim 15 wherein the salt, after being made, is recovered in solid form before coating onto the inner cores.

24. The composition of claim 1 wherein the pellets are administered in a capsule coated with a mixture of a first copolymer of methacrylic acid and methylmethacrylate and a second copolymer of methacrylic acid and methylmethacrylate, which disintegrate and release the pellets in the terminal ileum or in the colon following oral administration.

25. The composition of claim 24 wherein the first copolymer dissolves at pH 6 or greater and comprises about 48% methacrylic acid units per gram dry weight of first copolymer and wherein the second copolymer dissolves at pH 7 or greater and comprises about 29% methacrylic acid units per gram dry weight of second copolymer.

26. The composition of claim 25 wherein the ratio of first polymer to second polymer in the mixture is between 100:0 and 20:80.

27. The composition of claim 25 wherein the capsule coating has a thickness between about 150 and 200 μm.

28. The composition of claim 25 wherein the capsule coating has a thickness between about 80 and 120 μm.